REMARKS

Claims 18-45 are pending. Claims 23-27, 36-38, and 40-42 have been withdrawn from consideration. Claims 18-22, 28-35, and 39 are under examination. Claim 18 has been amended based on the Examiner's recommendations. The amendments serve to clarify the claimed invention and do not limit the claims. Claims 43, 44, and 45 have been added and are directed to particular species of interest, as supported in the specification at least on page 3. No new matter has been added.

Claim Rejections under 35 U.S.C. § 112

Claims 18-22, 28-35, and 39 are rejected under 35 U.S.C. § 112, second paragraph. Claim 18 has been amended as recommended by the examiner.

Claim 18, as amended, includes the language, *inter alia*, "...for a time and under conditions effective to inhibit neovascularization...". The prior claim included the language "administering to said subject ... an amount of a compound effective to inhibit neovascularization". For a compound to be administered in an amount effective to inhibit neovascularization, it must be administered under effective time and conditions. The time and conditions effective to inhibit neovascularization are inherent. This amendment is a clarification of the prior claim and is not limiting. In view of the clarifying amendment, Applicants respectfully request that this rejection be withdrawn.

Claim 18, as amended, includes the language, *inter alia*, "...wherein R' represents an alkyl group, an aryl group, an ester, an ether, an anhydride, or mixed alkyl/aryl derivative, or R', taken together with the alpha-amino group of glutamic acid, represents an amide, or an imide; R" represents an alkyl group, an ether, an aryl group, or mixed alkyl/aryl derivative, or R", taken together with the carbonyl group of tryptophan represents an amide, an imide, an ester, or an anhydride,...". These amendments are clarifications of the prior claims and are not limiting. In view of the clarifying amendment, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 18, 19, 21, 22, 28-35, and 39 are rejected under 35 U.S.C. § 103 over Haber (Prog. Biochem. Pharmacol. (1976), 12 (Drugs Affecting Renin-

Angiotensin-Aldosterone Syst., Prc. Kanematsu Conf. Kidney, 5th), 16-32) in view of Rodgers (USP 5,716,935). Applicants respectfully traverse this rejection.

Claim 18, as amended, is directed to a method of inhibiting neovascularization comprising administering to a subject in need thereof a pharmaceutical composition for a time and under conditions effective to inhibit neovascularization. The composition comprises a compound of the formula R'-Glu-Trp-R", wherein the formula weight of the compound is less than about 5000 Daltons.

Haber describes that EWPRFQIPP inhibits angiotensin-converting enzyme (ACE). Rodgers refers to neovascularization produced by angiotensin II and that angiotensin II stimulates angiogenesis in the chorio-allantoic membrane of the chick embryo.

A *prima facie* case of obviousness has not been established.

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143

Haber and Rodgers would not have suggested or motivated one to combine the reference teachings, since neither Haber nor Rodgers suggests that neovascular inhibition would be desirable. The Federal Circuit has held that "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." In re Gordon, 733 F.2d 900, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

Moreover, given the state of the art, a skilled artisan would not be motivated to combine the reference teachings, even if provided desirability. If combined, there was no reasonable expectation that a combination of the reference teachings would successfully achieve the claimed invention, given the state of the art. The Examiner states that "one of ordinary skill would have expected that an ACE inhibitor will inhibit neovascularization and angiogenesis." Applicants respectfully disagree. Although certain ACE inhibitors had been shown to inhibit

neovascularization, some ACE inhibitors had been shown to *stimulate* neovascularization and angiogenesis (See Appendix). "These results suggest that lisinopril [an ACE inhibitor] promoted angiogenesis." Cameron et al, Diabetologia, 1992, 35:12-18. Since one of ordinary skill could not have expected that an ACE inhibitor would inhibit neovascularization, it may only have been obvious to try. This is not the proper standard. MPEP § 2143.02. It would not have been obvious that it would work, as evidenced by the state of the art. Neither Haber nor Rodgers suggests or provides motivation to combine the reference teachings.

Finally, the cited prior art does not teach or suggest all the claim limitations, since neither document describes a method of inhibiting neovascularization.

In view of the arguments above, Applicants respectfully request that the rejection be withdrawn.

Applicants appreciate the Examiner's finding that claim 20 is free of prior art. In view of the amendments and arguments above, Applicants believe that all of the claims are now allowable.

In order to expedite prosecution, a terminal disclaimer will be filed upon a finding that the claims are otherwise allowable. A terminal disclaimer is not filed at this time since a new assignment is being prepared.

Applicants note the comments in the Office Action regarding the Information Disclosure Statement submitted May 2, 2002. References AT and AU are attached. Applicants note that the citation for AW already states that an abstract has been submitted. In view thereof, Applicants request an Examiner-initialled PTO-1449 be returned to Applicants including these three documents.

Under 37 C.F.R. § 1.34(a) and MPEP 402(a), the undersigned registered agent hereby signs this paper as an authorized representative of Melmotte, Inc., the current owner and purchaser of the patent estate of Cytran, Inc., the assignee of record in the file of this patent application. New assignment and Power of Attorney document are in progress transferring ownership of this pending application from Cytran Inc. to Melmotte, Inc. Small entity status is hereby claimed.

CONCLUSION

Applicants believe the application to be in condition for allowance, and respectfully request notice thereof at an early date. If any issues remain, the Examiner is encouraged to telephone the undersigned at the below-listed number.

Respectfully submitted,

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Date: Oct. 9, 2002

Attachment to Amendment

Marked Up Copy

Mark-up of Claims

18. A method of inhibiting neovascularization in a subject in need thereof comprising:

administering to said subject, for a time and under conditions effective to inhibit neovascularization, a pharmaceutical preparation comprising a pharmaceutically acceptable carrier and an amount of a compound effective to inhibit neovascularization with the formula of R'-Glu-Trp-R", or pharmaceutically acceptable salts thereof,

[wherein R' and R" is absent or a moiety independently selected from the group consisting of an amide, an imide, an ester, an anhydride, an ether, a methyl-alkyl ester, an ethyl-alkyl ester, an alkyl group, and an aryl group,]

wherein R' and/or R" is absent or

wherein R' represents an alkyl group, an aryl group, an ester, an ether, an anhydride, or mixed alkyl/aryl derivative,

or R', taken together with the alpha-amino group of glutamic acid, represents an amide, or an imide,

R" represents an alkyl group, an ether, an aryl group, or mixed alkyl/aryl derivative,

or R", taken together with the carbonyl group of tryptophan represents an amide, an imide, an ester, or an anhydride,

wherein R' can also represent an amide bond between the amine of said Glu and the side chain carboxylate of said Glu,

[wherein R' is present if R" is absent and R" is present if R' is absent,]

wherein both R', taken together with the alpha-amino group of glutamic acid, and R", taken together with the carbonyl group of tryptophan, are not both amide, and

wherein the formula weight of said compound is less than about 5000 Daltons.

43. The method of claim 18, wherein the ester is a methyl, ethyl, or other alkyl ester.

44. The method of claim 18, wherein neither R' nor R" contains amino acids.

45. The method of claim 18, wherein said composition consists essentially of L-Glu-L-Trp.